#33D

Mr. Coberly

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

001148

SUBJECT: Request for a residue tolerance of 0.6 ppm 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one (Sencor, Bay 94337) in or on potatoes.

DATE: October 18, 1974

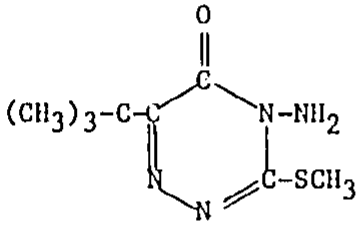
FROM:

TO: Tolerances Section
Coordination Branch
Registration Division (WH-567)

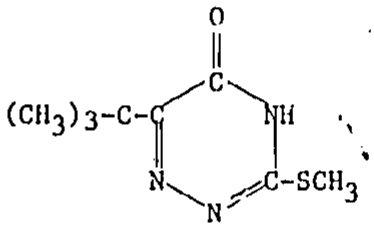
Pesticide Petition No.: 5F1559 - Chemagro
P.O. Box 4913
Kansas City, Missouri 64120

Related Petitions: 0G0940, 2F1274, 3G1368, 4F1432

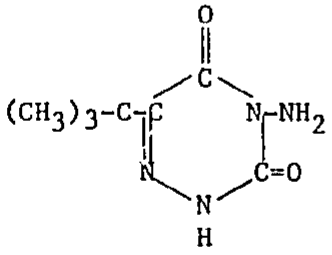
Chemical Structure (Sencor and 3 metabolites):



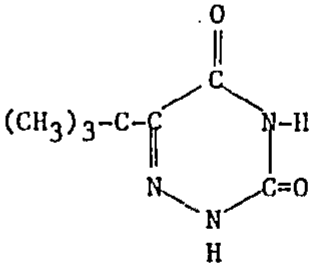
Sencor



DA



DK



DADK

Sencor and the three metabolites are present in potatoes at harvest mainly as water soluble conjugates.

EPA Form 1320-6 (Rev. 6-72)

001140

Formulations:

SENCOR 70% Wettable Powder

Active Ingredient:

4-Amino-6-(1,1-dimethylethyl)-3-(methylthio)-
1,2,4-triazin-5(4H)-one 70%

Inert Ingredients:

[redacted]

Technical Sencor contains 90% to 99% active ingredient. The remaining 1% to 10% consists of related organic compounds and reaction products. The Sencor content above is based on the active content not on the technical content. The adjustments for purity of the technical are made with the [redacted].

SENCOR (BAY 94337) 50% Wettable Powder

Active Ingredient:

4-Amino-6-(1,1-dimethylethyl)-3-(methylthio)-
1,2,4-triazin-5(4H)-one 50%

Inert Ingredients:

[redacted]

100.0%

Technical SENCOR contains 90% to 99% active ingredient. The remaining 1% to 10% consists of related organic compounds and reaction products. The Sencor content above is based on the active content not on the technical content. The adjustments for purity of the Technical are made with the [redacted].

Inerts are cleared as follows:

* Cleared under 180.1001(c)

** Cleared under 180.1001(c) and (e)

001148

Toxicological Evaluation:

Acute Oral Toxicity

Technical (20% EtOH/80% propylene):

Rat (F)	LD_{50}	1937 mg/kg
Guinea pig (M)	LD_{50}	198 mg/kg
Guinea pig (F)	LD_{50}	274.5 mg/kg

Technical (water emulsion):

Rat (M)	LD_{50}	2200 mg/kg
Rat (F)	LD_{50}	2345 mg/kg
Mouse (M&F)	LD_{50}	698-710 mg/kg
Guinea pig (M)	LD_{50}	> 250 mg/kg
Rabbit	LD_{50}	> 500 mg/kg
Cat	LD_{50}	> 500 mg/kg
Chicken	LD_{50}	> ~~100 mg/kg~~ should read 1,000 mg/kg

70% WP:

Rat (F)	LD_{50}	> 1400 mg/kg
Rat (M)	LD_{50}	> 2000 mg/kg
Quail	LD_{50}	> 500 mg/kg

50% WP:

Rat (M)	LD_{50}	4000 mg/kg ✓
Rat (F)	LD_{50}	4753 mg/kg ✓

Acute Dermal Toxicity

Technical (24 hr. contact)

Rabbit	LD_{50}	> 20,000 mg/kg

Technical (24 hr. contact w/abraded skin)

Rat	LD_{50}	> 20,000 mg/kg ✓

70% WP (24 hr. contact)

Rabbit	LD_{50}	> 20,000 mg/kg

50% WP (24 hr. contact)

Rabbit	LD_{50}	> 20,000 mg/kg
Rat	LD_{50}	> 20,000 mg/kg

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Acute Inhalation Toxicity:

Technical (60 min. exposure)

Rat	LC_{50}	> 20,000 µg/l

70% WP (60 min. exposure)

Rat	LC_{50}	> 160,000 µg/l

50% WP (60 min. exposure)

Rat	LC_{50}	> 20,000 µg/l

Skin Sensitivity:

Technical (500 mg for 72 hrs)

Rabbit	-	Slight erythema and edema on abraded skin

Technical (impregnated cotton pads/7 days)

Rabbit	-	No effect

Technical (impregnated cotton pads/24 hrs)

Human	-	No effect

50% WP (500 mg/72 hrs)

Rabbit	-	Slight erythema and edema on abraded skin

Eye Irritation:

Technical (50 mg)

Rabbit	-	No effect

Technical (100 mg/72 hrs)

Rabbit	-	Slight erythema in some animals after 24 hrs

50% WP (100 mg/72 hrs)

Rabbit	-	No effect

Subacute Toxicity:

90-Day Rat Feeding (TECH) - NEL 150 ppm
90-Day Dog Feeding (TECH) - NEL 150 ppm

Mutagenic Study:

Sencor Technical is not mutagenic for mice at levels up to 20 mg/kg

Acute Oral Toxicity of Metabolites:

DA Sencor (50% WP) LD_{50} > 275, < 300 mg/kg
DK Sencor (20% EtOH/80% propylene) LD_{50} > 600, < 900 mg/kg

18 Month Carcinogenicity Study (Mice)

There were no signs of tumor formation either grossly or microscopically in Swiss white mice fed Sencor at levels of 1250 and 2500 ppm for 18 months.

Two Year Chronic Feeding Studies (Sencor)

A. 2 Year Dog

6 month interim report (PP# 3G1368)

Four to 6 month old beagle dogs were individually housed and fed levels of 0, 25, 100 and 1500 ppm, each dose group contained 4 males and 4 females.

Three animals died at the 1500 ppm level, 2 males and 1 female. All three were reported to have died with severe foamy pneumonia. Both males were reported to exhibit severe emaciation but other organs were reported to show no symptoms. The mucous membranes of the intestine of the female were reported to be red and some parts of the intestine contained chyme mixed with blood. It was estimated that 100 ppm is the no-effect dose level.

24 month final report (PP# 5F1559)
Institut für Toxikologie, Report No. 4887,
September 24, 1974.

In dietary concentrations of 0, 25 and 100 ppm, Sencor produced no noticable effect on body weight, mortality, food consumption, hematology, liver function, kidney function, blood sugar and cholesterol levels, or adrenal glands.

The dietary concentration of 1500 ppm resulted in reduced weight gain, caused loss of body weight in some cases, proved lethal in 6 out of 8 dogs, produced noticeable hematological changes (increased sedimentation rates, lower erythrocyte counts, low Hb concentration, increased reticulocyte count), extramedullary hematopoiesis, liver damage (as a result of the increased destruction of erythrocytes caused by hypoxemia), kidney damage (necrosis of tubular epithelium), hyperglycemia and temporary hypercholesteraemia, altered adrenal gland function, and symptoms of testicular and prostate immaturity.

Based on the data submitted, an NEL of 100 ppm is confirmed in the final report.

B. 2 Year Rat

6 month interim report (PP# 3G1360)

Forty-five male and 45 female Wistar rats per group were fed levels 0, 25, 35, 100 and 300 ppm. Similar examination were made to those in the dog study reported previously.

Results

Food consumption and body weights were compared with the controls. None of the levels fed have shown any adverse effects on any of the parameters tested. These results show that in the rat the no-effect level is 300 ppm.

24 month final report (PP# 5F1559)
Institut für Toxikologie, Report No. 4888,
September 25, 1974.

Each test group (25, 35, 100 and 300 ppm) consisted of 40 male and 40 female Wistar rats. The control group (0 ppm) comprised 80 males and 80 females. The data submitted (hematological tests, liver function, urinalyses and kidney function, blood sugar and cholesterin, thyroid function, autopsy data and histopathological examination) supports the finding for an NEL of 300 ppm. There was no treatment or dose dependent response found in any of the parameters investigated.

Three Generation Rat Reproduction - Bayer AG - September 24, 1974

The material tested was identified as technical grade compound (Sdg 1603/71, 99.5%).

Ten male and twenty female rats of the FB30 strain (Elberfeld breed) were used for the F_0 generation at levels of 0, 35, 100, 300 ppm.

Results: The levels of 35, 100 and 300 ppm did not effect the fertility, lactation or reproductive performance of the various generations.

The no-effect level for this study is 300 ppm.

001148

Teratogenic Study (Bio-Test 1971
IBT No. J9027-
Chemagro #30172)

New Zealand doe rabbits

Exposure Scheme

Outline of Experiment

Group	Test Material	Dose Levels (mg/kg body weight/day)	Number of Females Inseminated	Number of Pregnant Animals
C-1	None	None	15	11
C-11	None	None	15	11
PC-1	Thalidomide	37.5	15	9
PC-11	Thalidomide	37.5	15	10
T-1	Bay 94337 Technical	7.5	15	9
T-11	Bay 94337 Technical	15.0	15	11

Test material was given orally by gelatin capsule from gestation day 6 through day 18 inclusive.

Observation included: daily checks for toxicity signs, body weights of does on gestation day 0, 6, 9, 12, 15, 13 and at sacrifice (day 29), examination of young at sacrifice of dam (weight and viability), gross examination (dissection) after alcohol fixation, and alizarin staining of skeleton.

Results: The observations did not reveal that Sencor produced terata in the exposed rabbits.

001148

Teratogenicity Study (Bio-Test 1972 11/21
IBT No. J1815
Chemagro #35159) 11282

New Zealand doe rabbits ✓

Exposure Scheme

Teratogenic Study - Albino Rabbits

Outline of Experiment

Test Material	Dose Levels (mg/kg body weight/day)	Number of Females Inseminated	Number of Pregnant Animals
None	-	17	11
None	-	17	13
Thalidomide	37.5	27	16
Thalidomide	37.5	17	14
Sencor (Bay 94337)	0.3	17	12
Sencor (Bay 94337)	2.0	17	10
Sencor (Bay 94337)	4.0	17	12
Sencor (Bay 94337)	8.0	17	13
Sencor (Bay 94337)	15.0	17	14
Sencor (Bay 94337)	30.0	17	15

Observations: (As for IBT No. J9027, Chemagro #30172)

Results: The observations did not reveal that Sencor produced terata in the exposed rabbits.

Teratogenicity Study (Bayer 1972
Report No. 3678
Chemagro #35073)

Pregnant female rats (FB30 strain) were dosed by stomach tube from the 6th to the 15th day of gestation with 0, 5, 15, 50 or 100 mg/kg of Sencor. Numbers of pregnant rats in treated groups were 21-22. Fetuses were caesarean delivered on the 20th day of gestation.

Observations for effects included external and internal gross examination, and alizarin red staining of skeletons.

Results: The observations did not reveal Sencor produced terata in the exposed rats.

001148

Summary

This additional toxicity data illustrated negative teratogenesis in the rabbit at 30 mg/kg/day - highest level tested; and in the rat at 100 mg/kg/day - highest level tested. Negative mutagenic activity was established in the rat with an NEL of 300 ppm. Twenty-four month rat feeding study demonstrated an NEL of 300 ppm. Twenty four month dog feeding study demonstrated an NEL of 100 ppm.

Findings/Recommendations

TB finds that the data in the petition supports the safety of the proposed tolerance of Sencor in or on potatoes at 0.6 ppm.

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cc: CB
EEEB
Division File
Branch Reading File
PP# 5F1559

R/D Init:CHWilliams:10/17/74
RBJaeger:RDCoberly:GEWhitmore:ssr:10/18/74
Init:CHWilliams

10/18/74